

I claim:

1. A method for generating a library of bi-ligands, comprising

(a) determining a common ligand to a conserved
5 site in a receptor family;

(b) attaching an expansion linker to said common ligand, wherein said expansion linker has sufficient length and orientation to direct a second ligand to a specificity site of a receptor in said
10 receptor family, to form a module; and

(c) generating a population of bi-ligands comprising a plurality of identical modules attached to variable second ligands.

2. The method of claim 1, further comprising:

(d) screening said population of bi-ligands
15 for binding to a receptor in said receptor family; and

(e) identifying a bi-ligand that binds to and has specificity for said receptor.

3. The method of claim 1, wherein said
20 population comprises three or more bi-ligands.

4. The method of claim 3, wherein said population comprises five or more bi-ligands.

5. The method of claim 1, wherein said receptor is an enzyme selected from the group consisting of kinases, dehydrogenases, oxidoreductases, GTPases, carboxyl transferases, acyl transferases, decarboxylases, transaminases, racemases, methyl transferases, formyl transferases, and α -ketodecarboxylases.

6. The method of claim 1, wherein said receptor family binds a cofactor selected from the group consisting of nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, thiamine pyrophosphate, flavin adenine dinucleotide, flavin mononucleotide, pyridoxal phosphate, coenzyme A, tetrahydrofolate adenosine triphosphate, guanosine triphosphate and S-adenosyl methionine.

7. The method of claim 1, wherein said expansion linker has approximate C2 symmetry.

8. The method of claim 7, wherein said expansion linker has perfect C2 symmetry.

9. A method for identifying a population of bi-ligands to receptors in a receptor family, comprising

(a) determining a common ligand to a conserved site in the receptor family;

(b) attaching an expansion linker to said common ligand, wherein said expansion linker has sufficient length and orientation to direct a second ligand to a specificity site of a receptor in said receptor family, to form a module; and

(c) generating a population of bi-ligands, wherein said bi-ligand comprises said module and a second ligand linked by said expansion linker.

10. The method of claim 9, further comprising:

5 (d) screening said population of bi-ligands for binding to a receptor in said receptor family;

(e) identifying a bi-ligand that binds to and has specificity for said receptor; and

10 (f) repeating steps (d) and (e) to identify a bi-ligand that binds to and has specificity for a second receptor in said receptor family.

11. The method of claim 9, wherein said receptor is an enzyme selected from the group consisting of kinases, dehydrogenases, oxidoreductases, GTPases, carboxyl transferases, acyl transferases, decarboxylases, transaminases, racemases, methyl transferases, formyl transferases, and α -ketodecarboxylases.

12. The method of claim 9, wherein said receptor family binds a cofactor selected from the group consisting of nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, thiamine pyrophosphate, flavin adenine dinucleotide, flavin mononucleotide, pyridoxal phosphate, coenzyme A, tetrahydrofolate adenosine triphosphate, guanosine triphosphate and S-adenosyl methionine.

13. The method of claim 9, wherein said expansion linker has approximate C2 symmetry.

14. The method of claim 13, wherein said expansion linker has perfect C2 symmetry.

15. A method for identifying a bi-target ligand to a receptor, comprising

- 5 (a) identifying a first bi-ligand to a first receptor in a receptor family, wherein said bi-ligand comprises a common ligand to a conserved site in a receptor family and a first specificity ligand to said first receptor;
- 10 (b) identifying a second bi-ligand to a second receptor in said receptor family, wherein said bi-ligand comprises said common ligand and a second specificity ligand to said second receptor; and
- 15 (c) generating a bi-target ligand comprising said common ligand, said first specificity ligand and said second specificity ligand, whereby said bi-target ligand can bind to said first receptor and said second receptor.

20 16. The method of claim 15, wherein said receptor is an enzyme selected from the group consisting of kinases, dehydrogenases, oxidoreductases, GTPases, carboxyl transferases, acyl transferases, decarboxylases, transaminases, racemases, methyl transferases, formyl transferases, and α -ketodecarboxylases.

17. The method of claim 15, wherein said receptor family binds a cofactor selected from the group consisting of nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, thiamine
5 pyrophosphate, flavin adenine dinucleotide, flavin mononucleotide, pyridoxal phosphate, coenzyme A, tetrahydrofolate adenosine triphosphate, guanosine triphosphate and S-adenosyl methionine.

18. The method of claim 15, wherein said
10 expansion linker has approximate C2 symmetry.

19. The method of claim 18, wherein said expansion linker has perfect C2 symmetry.

20. A library of bi-ligands comprising a common ligand to a conserved site in a receptor family
15 and an expansion linker attached to said common ligand, wherein said expansion linker has sufficient length and orientation to direct a second ligand to a specificity site of a receptor in said receptor family to form a module; and a specificity ligand attached to said
20 expansion linker.

21. The library of claim 20, wherein said population comprises three or more bi-ligands.

22. The library of claim 20, wherein said population comprises five or more bi-ligands.

23. The library of claim 20, wherein said receptor is an enzyme selected from the group consisting of kinases, dehydrogenases, oxidoreductases, GTPases, carboxyl transferases, acyl transferases, decarboxylases, transaminases, racemases, methyl transferases, formyl transferases, and α -ketodecarboxylases.

24. The library of claim 20, wherein said receptor family binds a cofactor selected from the group consisting of nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, thiamine pyrophosphate, flavin adenine dinucleotide, flavin mononucleotide, pyridoxal phosphate, coenzyme A, tetrahydrofolate adenosine triphosphate, guanosine triphosphate and S-adenosyl methionine.

25. The library of claim 23, wherein said expansion linker has approximate C2 symmetry.

26. The library of claim 25, wherein said expansion linker has perfect C2 symmetry.

27. A population of two or more bi-ligands, comprising:

(a) at least one bi-ligand to a first receptor comprising a common ligand to a conserved site in a receptor family and a specificity ligand to a specificity site of said first receptor in said receptor family; and

(b) at least one bi-ligand to a second receptor comprising said common ligand and a specificity ligand to a specificity site of said second receptor in said receptor family,

wherein said common ligand and said specificity ligand are linked by an expansion linker of sufficient length and orientation to direct said specificity ligand to a specificity site of said receptor.

5 28. The population of two or more bi-ligands of claim 27, wherein said receptor is an enzyme selected from the group consisting of kinases, dehydrogenases, oxidoreductases, GTPases, carboxyl transferases, acyl transferases, decarboxylases, transaminases, racemases,
10 methyl transferases, formyl transferases, and α -ketodecarboxylases.

 29. The population of two or more bi-ligands of claim 27, wherein said receptor family binds a cofactor selected from the group consisting of
15 nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, thiamine pyrophosphate, flavin adenine dinucleotide, flavin mononucleotide, pyridoxal phosphate, coenzyme A, tetrahydrofolate adenosine triphosphate, guanosine triphosphate and S-adenosyl
20 methionine.

 30. The population of two or more bi-ligands of claim 27, wherein said expansion linker has approximate C2 symmetry.

 31. The population of two or more bi-ligands
25 of claim 30, wherein said expansion linker has perfect C2 symmetry.

 32. A bi-target ligand, comprising:

(a) a common ligand to a conserved site in a receptor family;

(b) a first specificity ligand to a specificity site of a first receptor in said receptor family; and

(c) a second specificity ligand to a specificity site of a second receptor in said receptor family,

wherein said common ligand and said specificity ligands are linked by an expansion linker of sufficient length and in an orientation directing said first specificity ligand to said specificity site of said first receptor and said second specificity ligand to said specificity site of said second receptor.

33. The bi-target ligand of claim 32, wherein said receptor is an enzyme selected from the group consisting of kinases, dehydrogenases, oxidoreductases, GTPases, carboxyl transferases, acyl transferases, decarboxylases, transaminases, racemases, methyl transferases, formyl transferases, and α -ketodecarboxylases.

34. The bi-target ligand of claim 32, wherein said receptor family binds a cofactor selected from the group consisting of nicotinamide adenine dinucleotide, nicotinamide adenine dinucleotide phosphate, thiamine pyrophosphate, flavin adenine dinucleotide, flavin mononucleotide, pyridoxal phosphate, coenzyme A, tetrahydrofolate adenosine triphosphate, guanosine triphosphate and S-adenosyl methionine.

35. The bi-target ligand of claim 32, wherein said expansion linker has approximate C2 symmetry.

Year	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100
1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	